


PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference V7/002-V004/		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP98/03193	International filing date (day/month/year) 28/05/1998	Priority date (day/month/year) 02/06/1997	
International Patent Classification (IPC) or national classification and IPC C07K14/71			
Applicant VLAAMS INTERUNIVERSITAIR INSTITUUT... et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 14/12/1998		Date of completion of this report 1 5.09.99	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Merlos-Lange, A.M. Telephone No. +49 89 2399 8559	



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-42 as originally filed

Claims, No.:

1-22 as originally filed

Drawings, sheets:

1 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

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2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☒ all parts.
- ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1, 3, 6, 7, 12, 18, 19, 22
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-15, 18, 19, 22
Industrial applicability (IA)	Yes:	Claims see sep. sheet
	No:	Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
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VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1). Section IV

The IPEA concurs with the objection put forward by the ISA as to lack of unity of the present application according to Rule 13.1 PCT. The different groups of inventions which are not linked by a common special technical feature so as to form a single inventive concept are as follows:

a) Claims 1-15, 20, 22

SMAD interacting proteins such as SIP1, encoding nucleotide sequences, corresponding pharmaceutical compositions, diagnostic methods and transgenic animals, method for post-transcriptional regulation of gene expression by modulating SMAD interaction

b) Claim 16, 17, 21

SMAD interacting proteins having the characteristics of SIP2, corresponding sequences

c) Claim 18

Nucleic acid sequence encoding SIP7 or a functional fragment thereof

d) Claim 19

Nucleic acid sequence encoding SIP5 or a functional fragment thereof

The International Search Report covers all claims, therefore, examination is carried out for all claims 1-22.

2). Section V

Claim 1 is not sufficiently precise defined as required by Art. 6 PCT. The term "interacting" does not convey any precise functional, let alone any technical meaning. However, in the absence of clear technical features, the SMAD interacting proteins described in the prior art as for example in "Nature, vol. 383, no. 6602, 1996, 691-696, Chen,X. et al." or in "J. of Biol. Chem., vol. 272, no. 21, 1997, 13690-13696, De Chaestecker et al." fall within the scope of claim 1. It is further noted that a product is not necessarily rendered novel if it is obtainable by means of a particular process, unless the product is affected in a structural

manner.

Said claim as well as claim 12 are therefore not novel and inventive within the meaning of Art. 33(2), (3) PCT.

Claims 3, 6, 7, 18 and 19 do not appear to be novel and inventive in view of DATABASE EMBL EST 16, Acc. No. AA125512, 1996, DATABASE EMBL EMROD, Acc. No. M89802, 1992 and DATABASE EMBL EST16, Acc. No. AA212269, 1997. Said claims involve nucleic acid sequences comprising sequences which encode functional fragments of the SMAD interacting protein. It is not known whether the disclosed sequences exhibit a particular function. They nonetheless anticipate the claimed matter insofar as the additional functional characterisation of the sequences is considered no more than the additional definition of an already known entity. In other words, a known product does not regain novelty if it is additionally defined by a different feature. Furthermore, as already pointed out above, the term "interacting" does not define a particular and clear function. It is noted that merely for SIP1, at least the SMAD Binding Domain was determined (see page 13).

In view of the above, dependent claims 3-11, 13-15 and independent claims 12 and 22 are not considered to involve an inventive aspect as well, insofar as the subject-matter claimed is not characterised by additional particular features which would render it inventive in the sense of Art. 33(3) PCT (e.g. diagnosing which particular disease ??).

3). Section VIII

In the absence of a precise functional definition of the SMAD interacting proteins, the term "functional fragment thereof" is not clear (Art. 6 PCT, see above).

Claim 2 lacks the full meaning of the abbreviation "czf".

Claims 1, 2 and 21 refer to matter not defined by a single technical feature which is also clearly in contrast to the requirements of Art. 6 PCT.

Method claims 12 and 22 appear incomplete and unclear insofar as not a single procedure step is involved. Furthermore, the claims do not even precisely refer to SMAD proteins of the application.

**WRITTEN OPINION
SEPARATE SHEET**

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Part of the claims (10-13, 15, 22) which refer to the use of the SMAD proteins for a therapeutic and/or diagnostic purpose are not considered to be sufficiently supported and disclosed by the description (Articles 5 and 6 PCT). There is not at least one single example demonstrating the successful use of the SMAD interacting protein for example in the method of claim 22.

4). Section VI

This preliminary report is established on the opinion that the application enjoys a valid priority. In case of an invalid priority, document "DATABASE EMBL EMHUM1: "Homo sapiens mRNA for KIAA0569 protein, Acc, No. AB011141, 10.04.1998" may become relevant for the assessment of novelty and inventive step, when the application enters the European phase.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference V7/002-V004/	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 98/ 03193	International filing date (day/month/year) 28/05/1998	(Earliest) Priority Date (day/month/year) 02/06/1997

Applicant

VLAAMS INTERUNIVERSITAIR INSTITUUT VOORet al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☒ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

☒ filed with the international application.

☐ furnished by the applicant separately from the international application.

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. _____ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15, 20, 22

Smad interacting proteins such as SIP1, encoding nucleotide sequences, corresponding pharmaceutical compositions diagnostic methods and transgenic animals, method for post-transcriptional regulation of gene expression by modulating Smad interaction.

2. Claims: 16, 17, 21

Smad interacting proteins having the characteristics of SIP2, corresponding sequences.

3. Claim: 18

Nucleic acid sequence encoding SIP7 or a functional fragment thereof.

4. Claim: 19

Nucleic acid sequence encoding SIP5 or a functional fragment thereof.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/46 A61K31/70 A61K38/17 C12Q1/68
G01N33/566 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN X ET AL: "A transcriptional partner for MAD proteins in TGF-beta signalling" NATURE, vol. 383, no. 6602, 24 October 1996, pages 691-696, XP002047848 cited in the application see paragraph bridging pages 691 and 692 ---	1,12
X	DATABASE EMBL EST 16: "Mus musculus cDNA clone 584313 5' DNA-binding protein" ACCESSION NO AA125512, 26 November 1996, XP002084026 compare nucleotides 1-461 of AA125512 with nucleotides 1567-2027 in SEQ ID NO:1 --- -/--	3,6,7

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

° Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

11 November 1998

Date of mailing of the international search report

27/11/1998

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE CAESTECKER M P ET AL.: "Characterization of functional domains within Smad4/DPC4" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 21, 23 May 1997, pages 13690-13696, XP002084021 MD US see page 13690 ---	1
X	LAGNA G ET AL: "Partnership between DCP4 and SMAD proteins in TGF-beta signalling pathways" NATURE, vol. 383, no. 6603, 31 October 1996, pages 832-836, XP002047850 cited in the application see the whole document ---	1
X	MEERSSEMAN G ET AL: "The C-terminal domain of MAD-like signal transducers is sufficient for biological activity in the Xenopus embryo and transcriptional activation" MECHANISMS OF DEVELOPMENT, vol. 61, no. 1/02, January 1997, pages 127-140, XP002047849 cited in the application see the whole document ---	1
A	DATABASE EMBL HUM1: "Human mRNA for KIAA0150 gene, partial cds." ACCESSION NUMBER D63484, 3 August 1996, XP002084022 compare nucleotides 1-2908 of D63484 with nucleotides 38-2952 in SEQ ID NO:3 ---	16, 17, 21
X	DATABASE EMBL EMROD: "Mouse Wnt-7b mRNA, complete cds." ACCESSION NUMBER M89802, 3 April 1992, XP002084023 cited in the application compare nucleotides 74-529 in M89802 with nucleotides 391-848 in SEQ ID NO:8 ---	18
X	DATABASE EMBL EST16: "Stratagene mouse melanoma. Mus musculus cDNA clone 651678 5'" ACCESSION NUMBER AA212269, 3 February 1997, XP002084024 cited in the application Compare nucleotides 1-432 of AA212269 with nucleotides 930-1362 in SEQ ID NO:10 ---	19

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	DATABASE EMBL EMHUM1: "Homo sapiens mRNA for KIAA0569 protein, complete cds." ACCESSION NUMBER AB011141, 10 April 1998, XP002084025 compare nucleotides 1250-4249 in AB011141 with nucleotides 8-3007 in SEQ ID NO:1 -----	1-7